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(54) Title: SYNTHESIS OF AROMATIC COMPOUNDS BY DIELS-ALDER REACTION ON SOLID SUPPORT

(57) Abstract

Methods for synthesizing compounds, e.g., aromatic heterocycles, by Diels-Alder reaction on solid support, are disclosed. Also disclosed are compounds immobilized on solid supports and libraries of compounds.

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SYNTHESIS OF AROMATIC COMPOUNDS BY DIELS-ALDER REACTION ON SOLID SUPPORT

Background of the Invention

Recent developments of polymer-supported chemistry have been driven by interest in the assembly of libraries of molecular diverse compounds for their use in various screening protocols (for reviews, see, e.g., (a) Moos, W.H. Green, G.D.; Pavia, M.R. *Annu. Rep. Med. Chem.* **1993**, 28, 315-324. (b) Thompson, L.A.; Ellman, J.A. *Chem. Rev.* **1996**, 96, 555-600. (c) Hermkens, P.H.H.; Ottenheijm, J.C.; Recs, D. *Tetrahedron* **1996**, 52, 4527-4554. (d) Gallop, M.A.; Barret, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E.M. *J.Med. Chem.* **1994**, 37, 1233-1251. (e) Gordon, E.M.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gallop, M.A. *J.Med. Chem.* **1994**, 37, 1385-1401).

Aromatic compounds, e.g., aromatic heterocycles, including N-bearing heterocycles, are important compounds in fields including the agrichemical and pharmaceutical industries. For example, certain substituted pyridines have herbicidal activity (see, e.g., U.S. Patents 5,438,033 and 3,495,969); histamine antagonists (see, e.g., U.S. Patent 5,432,175); fungicides (see, e.g., U.S. Patent 5,185,339); and ferroelectric liquid crystals (see, e.g., U.S. Patent 5,145,601); and as intermediates in synthesis. Thus, procedures for rapidly synthesizing and screening aromatic compounds, e.g., aromatic heterocycles for activity are of considerable importance in these and other fields.

Summary of the Invention

In general, the invention provides methods for synthesizing aromatic compounds, preferably aromatic heterocycles, e.g., N-bearing aromatic heterocycles. The methods involve reaction of a diene with a dienophile under conditions such that a Diels-Alder reaction occurs, and allowing an aromatic compound, e.g., an aromatic heterocycle, to form, wherein at least one of the diene or dienophile is immobilized to a solid support.

In one embodiment, the method comprises the steps of contacting an electron-rich dienophile with a diene under conditions such that a Dicls-Alder reaction occurs between the diene and the dienophile to form a Diels-Alder adduct and subjecting the Diels-Alder adduct to conditions such that said adduct decomposes to form a solid-supported aromatic heterocycle.

In certain embodiments, the aromatic heterocycle is bound to the solid support through a cleavable linkage, preferably an ester linkage. In certain embodiments, the

method includes the further step of releasing the aromatic heterocycle from the solid support by cleaving the cleavable linkage.

In another aspect, the invention provides a method for synthesizing an aromatic heterocycle such a diazine, e.g., an aromatic diazine, e.g., an aromatic 1,2-diazine; or triazine or pyridine. In one embodiment, the method includes the steps of reacting an electron-rich dienophile or a tetrazine bound to a solid support, under conditions such that a Diels-Alder reaction occurs between the dienophile and the tetrazine; and allowing the diazine to form. In certain embodiments, the dienophile is selected from the group consisting of enamines, enol ethers, alkynes and ynamines. In certain embodiments, the tetrazine is a 1,2,4,5-tetrazine and a 1,2,4-triazine.

In another aspect, the invention provides a method for synthesizing a substituted pyridine. The method includes the steps of reacting an electron-rich dienophile and a triazine bound to a solid support under conditions such that a Diels-Alder reaction occurs between the dienophile and the triazine and allowing the pyridine to form. In certain embodiments, the dienophile is selected from the group consisting of enamines, ynamines, enol ethers and alkynes. In certain embodiments, the triazine is a 1,2,4-triazine.

In another aspect, the invention provides a method for synthesizing a library of aromatic heterocycles. The method includes the steps of reacting a dienophile and a diene under conditions such that a Diels-Alder reaction occurs between the diene and the dienophile, wherein the diene comprises a heteroatom, and wherein at least one of the dienophile and the diene is provided as a variegated population; and allowing the library of aromatic heterocycles to form; wherein at least one of the diene and the dienophile is bound to a solid support.

Detailed Description of the Invention

The present invention relates generally to methods for synthesizing compounds and libraries of compounds, on a solid support, by use of the Diels-Alder reaction (e.g., inverse-electron demand Diels-Alder reaction) of an immobilized diene or dienophile. The inventive methods provide a convenient route to a variety of substituted heteroaromatic compounds.

The present invention required development and engineering of chemistry to effectively attach (load) the heterocyclic azadiene system onto the solid support. For example, as described in more detail *infra*, the present inventors have prepared differentiated 1,2,4,5-tetrazines and 1,2,4-triazines and engineered suitable linker technologies to immobilize the diene system to a solid support. It has been reported that

in certain cases, solid-supported reactions can differ from the solution-phase counterparts. For example, yields and regio- or stereochemical outcomes of the reactions may differ according to whether the reaction is performed in solution or on a solid support. The present inventors have found conditions suitable for performing versatile Diels-Alder reactions in good yield in solid-supported formats. The successful implementation of this reaction methodology provides new and efficient ways to generate libraries of N-bearing heterocycles in a combinational format.

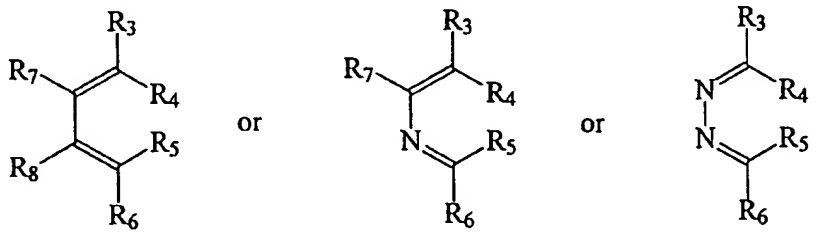
The term "Diels-Alder reaction" is art-recognized and refers to a [4+2] cycloaddition reaction between a diene (generally a compound having two conjugated double bonds) and a dienophile (generally a compound having at least one double or triple bond) (for a review, see, e.g., Brieger and Bennett, *Chem. Rev.* 80, 63-97 (1980)). In general, a Diels-Alder reaction produces a product having a newly-formed six-membered ring, although the product may spontaneously decompose or rearrange to produce a new compound, e.g., by extrusion of nitrogen, elimination and aromatization, and the like.

The term "inverse-electron demand Diels-Alder reaction" is art recognized and as used herein refers to a Diels-Alder reaction in which the diene partner is electron poor, and the dienophile partner electron rich. Preferred Diels-Alder reactions for use in the invention are inverse-electron demand Diels-Alder reactions.

The term "heteroatom" is art-recognized and, as used herein, refers to atoms other than carbon and hydrogen. Preferred heteroatoms include, but are not limited to, N, O, P, and S.

Dienes

In general, the invention features reaction of a diene with a dienophile. A variety of dienes suitable for use in Diels-Alder reactions are known in the art, and/or can be selected by the ordinarily skilled artisan. In general, a diene suitable for use in the methods of the invention can be represented by the one of the structures:



in which R_3-R_8 are each independently substituent groups. Suitable substitutent groups include hydrogen or a substituted or unsubstituted group such as alkyl (which as used herein includes cycloalkyl), alkenyl, alkynyl, aryl, (including heteroaryl), alkoxyl, amino (including alkylamino, dialkylamino (including cyclic groups such as pyrrolidino), arylamino, and diarylamino), acylamino (including alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, and aryloxycarbonylamino), carboxyl, alkoxycarbonyl, aminocarbonyl, arylcarbonyl, heterocyclyl, cyano, halogen, alkylsulfonyl, arylsulfonyl, and the like. Lower alkyls (e.g., branched or unbranched alkyls having one to ten carbon atoms in the group, more preferably one to six carbon atoms), are preferred. Furthermore, R_4 and R_5, taken together with the 4-atom dienyl moiety to which they are attached, can join to form a carbocycle or heterocycle, thereby forming a cyclic diene, which can be aromatic. It will be understood that any of the groups R_3-R_8 can represent a bond or a linker to a solid support.

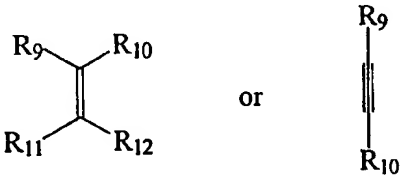
In general, a diene will be selected according to criteria such as: 1) the reactivity of the dienophile; 2) the reactivity of the diene; 3) the desired structure of the Diels-Alder product; and 4) the availability of the diene (e.g., commercial availability or synthetic accessibility).

In certain preferred embodiments, the diene is selected to be an electron-deficient diene, e.g., at least one of R_3-R_8 is an electron-withdrawing moiety, i.e., a group which withdraws electron density relative to a hydrogen atom. Electron-withdrawing groups are known in the art and include alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, cyano, and the like. Dienes having at least one electron-withdrawing group are preferred for inverse-electron demand Diels-Alder reactions. As described in Example 1, *infra*, substituents, e.g., R_3-R_8, can be derivatized with removable groups, e.g., protecting groups, to "tune" the electronic characteristics of the diene.

In preferred embodiments, the diene is a cyclic compound, e.g., a heterocyclic compound, e.g., a diazine, a triazine, or a tetrazine. In certain embodiments, the diene is an aromatic compound. In certain embodiments, the diene is selected such that Diels-Alder reaction of the diene with a dienophile will result in a compound capable of spontaneous extrusion of dinitrogen; accordingly, for example, in certain embodiments, the diene is a 1,2-diazine, a 1,2,4-triazine, or a 1,2,4,5-tetrazine. In certain embodiments, the diene is selected such that Diels-Alder reaction of the diene with a dienophile will result in a compound capable of spontaneous extrusion of another moiety, e.g., sulfur dioxide, carbon dioxide, or carbon monoxide. Accordingly, a diene can be, e.g., a 1,1-thiophene dioxide, a 2-pyrone, or a cyclopentadienone, respectively.

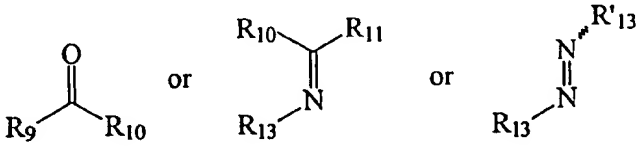
Dienophiles

A variety of dienophiles suitable for use in the Diels-Alder reactions are known in the art and/or can be selected by the ordinarily skilled artisan. In certain preferred embodiments, a dienophile can have the structure:



in which each of R_9-R_{12} is independently either a hydrogen or a substituted or unsubstituted group such as alkyl, alkoxy, alkenyl, alkynyl, aryl, (including heteroaryl), alkoxyl, amino (including alkylamino, dialkylamino (including cyclic groups such as pyrrolidino, arylamino, and diarylamino), acylamino (including alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, and aryloxycarbonyl), carboxyl, alkoxycarbonyl, aminocarbonyl, arylcarbonyl, heterocyclyl, cyano, halogen, and the like. Furthermore, R_{10} and R_{12}, taken together with the ethylene moiety to which they are attached, can join to form a carbocycle or heterocycle (preferably having from 4 to 8 atoms in the cyclic moiety), thereby forming a cyclic dienophile.

In certain other embodiments, a dienophile can be represented by one of the structures:



in which R_9-R_{11} are as defined above (preferably alkyl or aryl) and R_{13} and R'_{13} are independently alkyl, alkenyl, alkynyl, aryl, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, and aryloxycarbonyl. It will be understood that any of the groups R_9-R_{13} (in any of the embodiments described above) can represent a bond or a linker to a solid support.

In general, a dienophile will be selected according to criteria such as: 1) the reactivity of the dienophile; 2) the reactivity of the diene; 3) the desired structure of the Diels-Alder product; and 4) the availability of the dienophile (e.g., commercial availability or synthetic accessibility). In certain preferred embodiments, at least one of R_9-R_{12} is an electron-donating group, i.e., a group which releases electron density relative toa hydrogen atom. Examples of electron-donating groups include amino, acylamino, alkoxy, thioalkyl, and the like. Dienophiles having at least one electron-

donating group are preferred for inverse-electron demand Diels-Alder reactions. The skilled artisan will appreciate that substituents, e.g., R_8 -R_{13}, can be derivatized with removable groups, e.g., protecting groups, to "tune" the electronic characteristics of the dienophile.

In certain preferred embodiments, the groups R_9-R_{12} can be selected such that at least one of the moieties R_9-R_{12} can be eliminated (preferably spontaneously under the conditions of the Diels-Alder reaction) from the Diels-Alder product to produce a new product. For example, in the reactions described in Example 1, below, the initial Diels-Alder reaction is accompanied by extrusion of dinitrogen to produce an initial, non-aromatic heterocycle having a substituent such as a dialkylamino group (e.g., Table 1, entries 8a, b, d, e, and f) an acylamino group (e.g., Table 1, entry 8c), an alkoxy group (e.g., Table 1, entries 8g and h), and the like. These substituents can be eliminated under relatively mild conditions to produce an aromatic product; indeed, the eliminations in the examples given in Table 1 are spontaneous under the conditions employed, and the intermediate non-aromatic heterocycle is not isolated (although, in certain cases, the intermediate could be isolated, if desired).

Compounds useful as dienophiles include alkenes, enamines, ynamines, enol ethers (including silyl enol ethers), enol esters, thioenol ethers (and thioenol esters), ketene acetals, ketene dithioacetals, imidates, imines, alkynes, and the like. In certain embodiments, a dienophile can be a vinylstannane, a vinylsilane, a vinylphosphonate, and the like.

Diels-Alder Reactions

The methods of the invention involve the Diels-Alder reaction of a diene with a dienophile, wherein at least one of the diene and the dienophile is immobilized on a solid support. In cases in which the diene and the dienophile are both non-symmetrical, the Diels-Alder adduct (i.e., the immediate product of the Diels-Alder reaction) can have at least two possible structures, depending upon the regioselectivity of the Diels-Alder reaction (if any). For example, in the Diels-Alder reactions of Example 1, the use of an unsymmetrical dienophile with the unsymmetric diene 5 results in two products (e.g., after extrusion of nitrogen and elimination, aromatic products (Table 1)8d, 8g, and 8h are formed as mixtures with another regioisomer).

The regiochemistry of a Diels-Alder reaction can be affected by such factors as the steric bulk of the diene and the dienophile, and the stereoelectronic nature of the diene and the dienophile. Thus, alteration of the steric bulk and/or the stereoelectronic nature of either reaction partner can have an effect on the regiochemical outcome of the

Dicls-Alder reaction, and may also have an effect on the reaction rate. Compare, for example, product (Table 1) 8e with product (Table 2) 10e - the regiochemistry obtained is opposite, presumably due to the differing electronic nature of the dienes and dienophiles employed (i.e., enamine vs. alkyne, and thiomethyl diene vs. sulfonyl diene). Appropriate choice of diene and dienophile can thus affect the product of the reaction, and should be chosen to favor the desired product.

In the methods of the invention, the Diels-Alder reaction produces an initial product (or adduct) which is generally not aromatic, but can preferably be aromatized to produce an aromatic compound, e.g., by elimination as described herein. In preferred embodiments, the intermediate Diels-Alder adduct can be aromatized spontaneously under the conditions of the Diels-Alder reaction or conventional workup. However, in certain embodiments, the initial Diels-Alder adduct can be manipulated, e.g., further processed, derivatized, or reacted, to produce an aromatic compound.

Aromatic products

In general, the aromatic products produced according to the methods of the invention are unsubstituted or substituted compounds which include a six-membered aromatic ring. In certain preferred embodiments the aromatic compound is a substituted heterocyclic aromatic compound, e.g., a 1,2-diazine, a pyridine, a quinoline, and the like. In certain embodiments, the aromatic product can be a carbocycle, e.g., a substituted benzene, naphthalene, or the like. The aromatic product can be substituted with any of the groups R_3-R_{13} as defined herein. Thus, the methods of the invention provide ready access to a wide variety of aromatic compounds. It will be appreciated that the nature of the aromatic compound produced by the methods of the invention is determined largely by the diene and dienophile used for the Diels-Alder reaction, together with the reaction conditions employed for the Diels-Alder reaction and aromatization steps. The invention provides methods for synthesizing a variety of unsubstituted or substituted heterocycles, including pyridines, quinolines, diazines, quinazolines, and the like.

Linkers

At least one member of each diene/dienophile pair will be immobilized on a solid support. Accordingly, a diene or dienophile can be immobilized on a solid support through a direct bond to the support, or through a linker or spacer arm to the support. As described in Example 1, below, a linker arm, where employed, can conveniently be attached to, and/or cleaved from, the diene or dienophile and/or the solid support (i.e., is a cleavable linker), preferably under mild conditions, to permit the immobilization of a

diene or dienophile on the solid support, and the ready detachment of a product from the solid support, without causing undesirable side reactions of, e.g., the diene, dienophile, product, or solid support. A variety of linkers which may find use in the invention are known in the art, e.g., for the solid-phase synthesis of peptides or the combinatorial synthesis of non-peptide organic molecules.

Reaction conditions

The reactions of the present invention may be performed under a wide range of conditions, though it will be understood that the solvents and temperature ranges recited herein are not limitative and only correspond to a preferred mode of the process of the invention.

In general, it is desirable that reactions are run using mild conditions that will not adversely affect the diene, the dienophile, any intermediates, or the product. For example, the reaction temperature influences the speed of the reaction, as well as the stability of the reactants and catalyst. The reactions will usually be run at temperatures in the range of -78°C to 100°C, more preferably in the range -20°C to 50°C and still more preferably in the range -20°C to 25°C.

In general, the reactions according to the invention will be performed in a solvent, e.g., in solution or suspension. The reactions may be run in an inert solvent, preferably one in which the reaction ingredients, optionally including the polymeric support, are substantially soluble. Suitable solvents include ethers such as diethyl ether, 1,2-dimethoxyethane, diglyme, t-butyl methyl ether, tetrahydrofuran and the like; halogenated solvents such as chloroform, dichloromethane, dichloroethane, chlorobenzene, and the like; aliphatic or aromatic hydrocarbon solvents such as benzene, toluene, hexane, pentane and the like; esters and ketones such as ethyl acetate, acetone, and 2-butanone; polar aprotic solvents such as acetonitrile, dimethylsulfoxide, dimethylformamide and the like; or combinations of two or more solvents. Furthermore, in certain embodiments it may be advantageous to employ a solvent that is not inert to the substrate under the conditions employed, e.g., use of ethanol as a solvent when ethanol is desired as a reactant. In embodiments where water or hydroxide are not preferred as reactants, the reactions can be conducted under anhydrous conditions. In certain embodiments, ethereal solvents (e.g., diethyl ether, tetrahydrofuran (THF), dioxane, dimethoxyethane, and the like) are preferred.

In certain embodiments it is preferable to perform the reactions under an inert atmosphere of a gas such as nitrogen or argon.

In preferred embodiments, the reaction conditions are selected to permit isolation or purification of the Diels-Alder product, or a product resulting from rearrangement of the Diels-Alder adduct. For example, a soluble polymeric support conjugated to a Diels-Alder product can be precipitated by the addition of an inert nonsolvent, and the precipitate washed with an inert nonsolvent to remove, or reduce the amount of, impurities and unreacted materials. In another illustrative embodiment, an insoluble polymeric support conjugated to a Diels-Alder product can be separated from a reaction mixture by, e.g., filtration, and washed to remove, or reduce the amount of, impurities and unreacted materials (see, e.g., Example 1). The purified polymeric-support-bound product can then be further reacted or processed, if desired.

It is known that the reaction rate or stereochemical outcome of certain Diels-Alder reactions can be affected by the use of catalysts (such as Lewis acid catalysts, including, e.g., boron trifluoride etherate, aluminum chloride, $SnCl_4$, and the like). Accordingly, the invention contemplates the use of catalysts in the Diels-Alder reaction, where appropriate.

Solid Supports

The term "solid support," refers to a solid or insoluble moiety suitable for immobilization of a compound, and further reaction or purification of the immobilized compound.

Immobilization of a compound (e.g., a diene or a dienophile) to a solid support can be covalent or non-covalent (e.g., ionic, hydrophobic, magnetic, etc.). In a preferred embodiment, the compound is immobilized to a solid support through a covalent bond. In certain preferred embodiments, the solid support is a polymeric support. In certain embodiments, the solid support is in the form of discrete particles, e.g., polymer beads, although, as described herein, methods for attachment of a library of compounds to a spatial array on a surface or on supports such as polystyrene pins are known in the art and are contemplated for use in the methods and compositions of the invention.

Polymeric supports with appropriate functional groups are known in the art and can be prepared by known techniques. For example, polymers including the carboxylic acid chloride functionality (e.g., -COCl) are known (see, e.g., P. Hodge and D.C. Sherrington, "Polymer-supported Reactions in Organic Synthesis", Chapter 1, (1980)) and can be prepared by treatment of conventional polymer-supported carboxylic acids (e.g., polyacrylic acids) with, e.g., thionyl chloride, oxalyl chloride, and the like. Polymeric supports including sulfonyl chloride functionalities can be obtained by the reaction of a polymer including sulfonic acid moieties (e.g., $-SO_3H$) with, e.g., thionyl

chloride, or by other known methods, for example, the method described in U.S. Patent 5,118,766. Benzyl halide-containing polymers are well known and include chloromethylated polystyrene (e.g., Merrifield resin).

For ease of use and lower cost, it is desirable that the polymeric support be easily recyclable. In a preferred embodiment, the polymeric support can be regenerated and reused.

Soluble polymeric supports include functionalized polymers based on polyvinyl alcohol or polyethylene glycol (PEG). A soluble support can be made insoluble (e.g., can be made to precipitate) by addition of a suitable inert nonsolvent. One advantage of reactions performed using soluble polymeric supports according to the invention is that reactions in solution can be more rapid, higher yielding, and/or more complete than reactions that are performed on insoluble polymeric supports.

Insoluble polymeric supports include functionalized polymers based on polystyrene, polystyrene/divinylbenzene copolymers, and other polymers known to the skilled artisan. Non-resin-based solid supports include silica, functionalized silica, and the like; many silica-derived supports are commercially available.

Methods of Synthesis

In general, the invention provides methods for synthesizing aromatic compounds, preferably aromatic heterocycles, e.g., N-bearing aromatic heterocycles. The methods involve reaction of a diene with a dienophile under conditions such that a Diels-Alder reaction occurs, and allowing an aromatic compound, e.g., an aromatic heterocycle, to form, wherein at least one of the diene and dienophile is immobilized to a solid support.

In preferred embodiments, the diene is immobilized on the solid support. In preferred embodiments, the diene comprises a heteroatom; in certain embodiments, the diene is a heterocycle.

In another embodiment, the method comprises the steps of contacting an electron-rich dienophile with a diene under conditions such that a Diels-Alder reaction occurs between the diene and the dienophile to form a Diels-Alder adduct and subjecting the Diels-Alder adduct to conditions such that said adduct decomposes to form a solid-supported aromatic heterocycle. In preferred embodiments, the diene comprises a heteroatom; in preferred embodiments, at least one of the diene and the dienophile is bound to a solid support. In certain embodiments, the step of decomposing the Diels-Alder adduct comprises heating the Diels-Alder adduct. In certain embodiments, the

decomposing step comprises eliminating from the Diels-Alder adduct a leaving group selected from the group consisting of alcohols and amines.

In certain embodiments, the aromatic heterocycle is bound to the solid support through a cleavable linkage, preferably an ester linkage. In certain embodiments, the method includes the further step of releasing the aromatic heterocycle from the solid support by cleaving the cleavable linkage.

In another aspect, the invention provides a method for synthesizing a substituted pyridine. The method includes the steps of reacting an electron-rich dienophile and a triazine bound to a solid support under conditions such that a Diels-Alder reaction occurs between the dienophile and the triazine and allowing the pyridine to form. In certain embodiments, the dienophile is selected from the group consisting of enamines, ynamines, enol ethers and alkynes. In certain embodiments, the triazine is a 1,2,4-triazine.

In another aspect, the invention provides a method for synthesizing a diazine, e.g., an aromatic diazine, e.g., an aromatic 1,2-diazine. In one embodiment, the method includes the steps of reacting an electron-rich dienophile and a tetrazine, wherein either the dienophile or the tetrazine is bound to a solid support, under conditions such that a Diels-Alder reaction occurs between the dienophile and the tetrazine; and allowing the diazine to form. In certain embodiments, the dienophile is selected from the group consisting of enamines, enol ethers and alkynes. In certain embodiments, the tetrazine is a 1,2,4,5-tetrazine.

In another aspect, the invention provides a method for synthesizing a library of aromatic heterocycles. The method includes the steps of reacting a dienophile and a diene under conditions such that a Diels-Alder reaction occurs between the diene and the dienophile, wherein the diene comprises a heteroatom, and wherein at least one of the dienophile and the diene is provided as a variegated population; and allowing the library of aromatic heterocycles to form; wherein at least one of the diene and the dienophile is bound to a solid support. The term "variegated population" as used herein, refers to a population including at least two different chemical entities, e.g., of different chemical structure. For example, a "variegated population" of dienophiles would comprise at least two different dienophiles. Similarly, a variegated population of dienes comprises at least two different dienes. A "variegated population" can be employed in the combinatorial synthesis methods described above, e.g., as a mixture of compounds undergoing reaction in a single vessels, or as individual compounds employed in a plurality of reactions in a plurality of vessels.

According to methods of the invention, the Diels-Alder adduct, and, preferably, the aromatic product, are synthesized while immobilized on a solid support. Thus, the Diels-Alder adduct and/or the aromatic product can be readily processed, e.g., washed, purified, filtered, and the like, by methods known in the art, e.g., filtration and other physical separations. This has the advantage of easily providing purified compounds with expensive and time-consuming steps such as chromatography, crystallization, and the like (although, of course, such techniques can be used to purify compounds which have been cleaved from the solid support).

Libraries

In another aspect, the invention features substituted aromatic compounds (e.g., N-bearing heteroaromatic compounds); libraries of substituted aromatic compounds (e.g., N-bearing heteroaromatic compounds); methods for synthesizing aromatic compounds (e.g., N-bearing heteroaromatic compounds); and methods of synthesizing libraries of substituted aromatic compounds (e.g., N-bearing heteroaromatic compounds).

In one embodiment, the invention provides a library of aromatic heterocycles represented by the formula S-L-A, in which S is a solid support; L is absent or, if present, is a linking moiety; A is an aromatic heterocyclyl moiety. The solid support can be a polymer resin. In preferred embodiments, the aromatic heterocyclyl moiety is selected from the group consisting of pyridyl, 1,2-diazinyl, 1,3-diazinyl, and 1,4-diazinyl.

The synthesis of combinatorial libraries is well known in the art and has been reviewed (see, e.g., E.M. Gordon *et al.*, *J. Med. Chem.* 37:1385-1401 (1994)). The subject invention contemplates methods for synthesis of combinatorial libraries of compounds (e.g., aromatic compounds, e.g., N-bearing aromatic heterocycles). Such libraries can be synthesized according to a variety of methods. For example, a "split-pool" strategy can be implemented in the following way: beads of a functionalized polymeric support are placed in a plurality of reaction vessels. To each aliquot of beads is added a solution of a different diene (or dienophile), appropriately functionalized (with a linker, if desired) to be capable of reaction with, and immobilization to, the solid support, and the reactions proceed to yield a plurality of immobilized dienes (or dienophiles). The aliquots of derivatized beads are then washed, "pooled" (i.e., recombined), and the pool of beads is again divided, with each aliquot being placed in a separate reaction vessel. To each reaction vessel is added a solution of a different dienophile (or diene), and reaction occurs to yield a plurality of reaction vessels each

containing a plurality of substituted Diels-Alder reaction products (e.g., N-bearing aromatic heterocyles).

In another illustrative synthesis, a "diversomer library" is created by the method of Hobbs DeWitt *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 90:6909 (1993)). Aliquots of functionalized polymeric support beads are placed in an array of reaction vessels, and one of a plurality of dienes (or dienophiles), having a reactive group suitable for reaction with, and immobilization to, the solid support, is introduced into each vessel. After reaction, the beads are washed to yield an array vessels containing polymer-supported dienes (or dienophiles). Each vessel in the array is then reacted with one of a plurality of dienophiles (or dienes). After Diels-Alder reaction, purification and workup yields a soluble library of substituted Diels-Alder products.

Other synthesis methods, including the "tea-bag" technique of Houghten (see, e.g., Houghten *et al.*, *Nature* 354:84-86 (1991)) can also be used to synthesize libraries of compounds according to the subject invention.

Combinatorial libraries can be screened to determine whether any members of the library have a desired activity, and, if so, to identify the active species. Methods of screening combinatorial libraries have been described (see, e.g., Gordon *et al.*, *J Med. Chem.*, *op. cit.*). Soluble compound libraries can be screened by affinity chromatography with an appropriate receptor to isolate ligands for the receptor, followed by identification of the isolated ligands by conventional techniques (e.g., mass spectrometry, NMR, and the like). Immobilized compounds can be screened by contacting the compounds with a soluble receptor; preferably, the soluble receptor is conjugated to a label (e.g., fluorophores, colorimetric enzymes, radioisotopes, luminescent compounds, and the like) that can be detected to indicate ligand binding. Alternatively, immobilized compounds can be selectively released and allowed to diffuse through a membrane to interact with a receptor.

Combinatorial libraries of compounds can also be synthesized with "tags" to encode the identity of each member of the library (see, e.g., W.C. Still *et al.*, PCT Publication No. WO 94/08051). In general, this method features the use of inert, but readily detectable, tags, that are attached to the solid support or to the compounds. When an active compound is detected (e.g., by one of the techniques described herein), the identity of the compound is determined by identification of the unique accompanying tag. This tagging method permits the synthesis of large libraries of compounds which can be identified at very low levels.

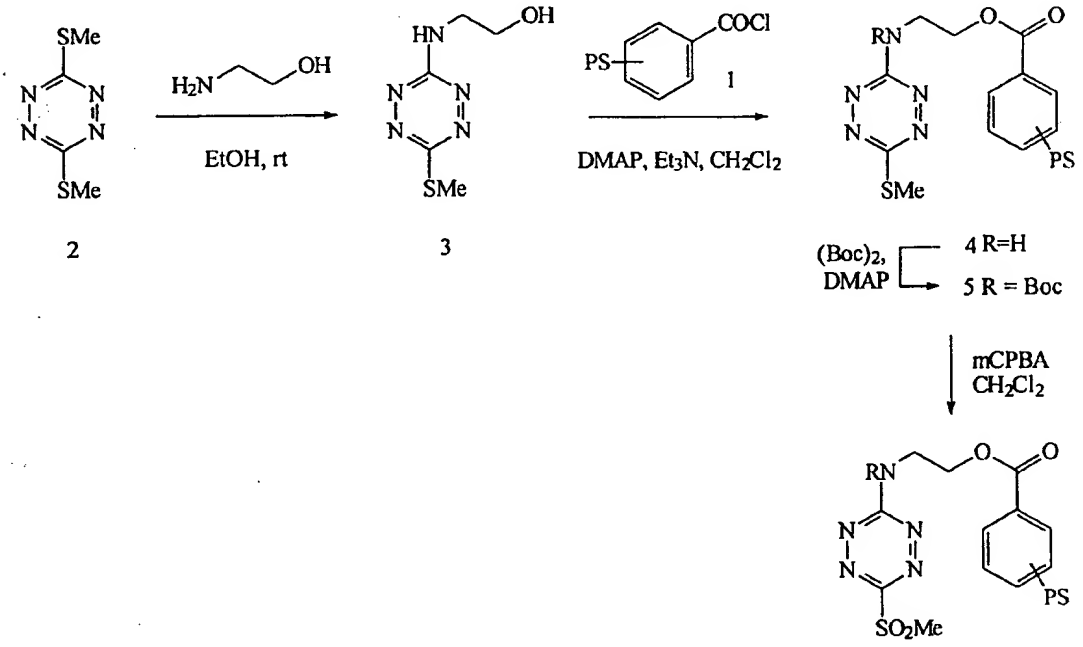
In preferred embodiments, the libraries of aromatic (e.g., heteroaromatic, e.g., N-bearing heteroaromatic) compounds of the invention contain at least 30 compounds,

more preferably at least 100 compounds, and still more preferably at least 500 compounds. In preferred embodiments, the libraries of N-bearing aromatic compounds of the invention contain fewer than 10^9 compounds, more preferably fewer than 10^8 compounds, and still more preferably fewer than 10^7 compounds.

The invention is further illustrated by the following non-limiting examples.

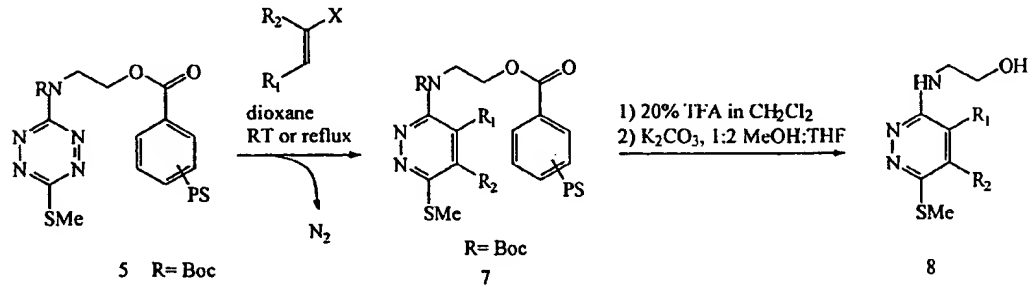
Example 1

The solution phase Diels-Alder reactions of heterocyclic azadienes (for reviews, see, e.g., (a) Boger, D.L. *Tetrahedron* **1983**, 39, 2869-2939. (b) Boger, D.L. *Chem. Rev.* **1986**, 86, 781-793. (c) Boger, D.L. Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis,* Academic Press, San Diego, **1987**, *Chapter 10*, pp. 300) is well established. In this Example, inverse electron demand Diels-Alder reactions of 3,6-substituted-1,2,4,5-tetrazines on a solid phase format are demonstrated. This reaction constructs functionalized 1,2-diazines which can display a high degree of a functional group diversity. The process should be readily adaptable to the preparation of small molecule libraries of N-bearing heterocycles that project functional group diversity displayed in an array of 180°, i.e., at four consecutive positions on the aromatic ring.



Scheme 1

The preparation of immobilized dienes is summarized in Scheme 1, and utilized the readily available 3,6-bis(thiomethyl)-1,2,4,5-tetrazine **2** (see, e.g., Boger, D.L.; Sakya, S.M. *J.Org. Chem.* **1988**, 53, 1415-1423). The tetrazine **2** was selected, at least in part, based on its easily replaceable thiomethyl groups, which provide easy access to suitable linkers as well as other functional groups at the C-3 and C-6 positions (see, e.g., Barlin, G.B.; Brown, W.V. *J. Chem. Soc. (C)* **1967**, 2473-2476). Nucleophilic aromatic substitution of one of the thiomethyl groups with amino-ethanol (1.2 equiv, EtOH, rt, 12 h) afforded the unsymmetrical tetrazine **3** in 97% yield bearing the four-atom tether. Carboxylated polystyrene resin **1** was prepared from Polystyrene-CO_2H (commercially available from Advanced ChemTech) with excess of $(COCl)_2$ (4.0 equiv) refluxing in dry benzene for 12 h. The resulting resin was washed with dry benzene under argon and dried *in vacuo* to afford the acid chloride **1** as a light brown colored solid (PS indicates the polymeric support). The tetrazine nucleus was next covalently linked to carboxylated polystyrene **1** through its acid chloride (cat. 4-dimethylaminopyridine (DMAP), Et_3N, CH_2Cl_2, rt, 48 h) to afford the immobilized amino tetrazine **4**. This material was made more electron deficient by the acylation of the secondary amine with $(Boc)_2O$ (4 equiv, cat. DMAP, THF, rt, 16 h) producing the N-Boc derivative **5** (Boc = t-butoxycarbonyl), which was followed by oxidation of the methyl sulfide to the sulfone with *m*-CPBA (2.5 equiv, CH_2Cl_2, rt, 6 h) to provide the fully elaborated, immobilized 3,6-disubstituted tetrazine complex **6** as a crimson-red solid with a loading efficiency greater than 90% for four steps (the loading yield is based on the loading level of carboxylic acid on the polystyrene-CO_2H, which is 2.5 mmol/g).

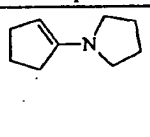
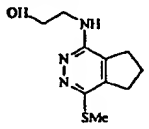
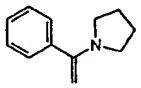
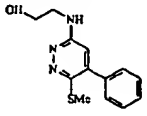
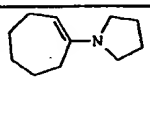
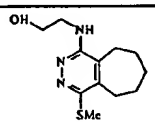
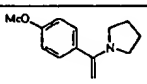
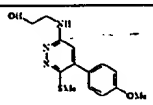
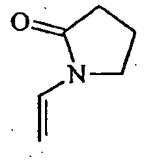
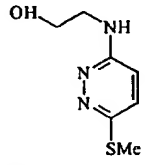
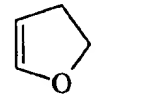
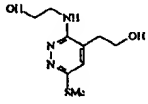
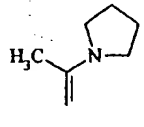
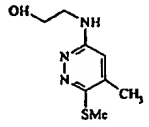
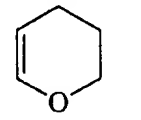
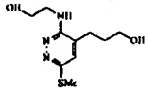


Scheme 2

The utility of azadiene complexes **5** and **6** as electron deficient dienes in the inverse electron demand Diels-Alder reaction was examined. The results of these studies are summarized in Tables 1 and 2. Azadiene complex **5** was reacted with various electron-rich olefins in dioxane at room or elevated temperature (see the conditions described in Example 3, below) to give the resin-bound cycloaddition product

7. To avoid the premature nucleophilic substitution at the C-6 position with OMe, the Boc group of **7** was removed with 20% TFA in CH_2Cl_2 before the product **8** was cleaved from the solid support by base hydrolysis (K_2CO_3, 1:2 MeOH-THF) (Scheme 2) (base promoted hydrolysis of **7** without removal of the Boc group resulted in the partial loss of Boc group and substitution of the -SMe with -OMe in the product, thus decreasing the purity of the product). A series of 3-amino-6-thiomethyl-1,2-pyridazines were synthesized in good to moderate overall yield and is based on the initial loading level of the carboxylic acid on polystyrene-CO_2H, and represents 6 steps (Table 1).

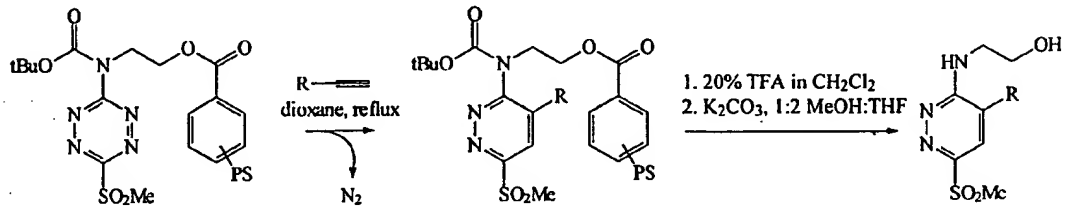
Table 1. Diels-Alder Reactions of Polymer Supported Azadiene **5**

Dienophile[a]	Product	Yield of 8[b]	Dienophile[a]	Product	Yield of 8[b]
		8a 82%			8e 35%
		8b 79%			8f 30%
		8c 61%			8g 47% ratio = 1:2[c]
		8d 67% ratio = 4:1[c]			8h 28% ratio = 2:1[c]

[a]Preparation of enamines: (1) Cyclic ketone: the pyrrolidino enamines were prepared in benzene with the aid of azeotropic removal of water (*cf.* Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovic, J.; Terrel, R. *J.Am. Chem. Soc.* **1963**, *85*, 207-222), (2) Acyclic ketone: the enamines were prepared in ethyl ether with the aid of 4-A molecular sieves. (*cf.* Taguchi, K.; Westheimer, F.H. *J. Org. Chem.* **1971**, *36*, 1570-1572) [b]The yields are based on the loading level of carboxylic acid on the polystyrene-CO_2H (6 steps overall).

[c]The ratio was determined by ^1H NMR (400 MHz) of the crude products. The regioisomers were assigned by ^1H NMR analysis.

Azadiene complex **6** bearing the sulfone group is more reactive than **5** in the Diels-Alder reactions as more efficient conversion is generally achieved with less reactive dienophiles (the reaction of tetrazine complex **5** with alkynes produced only trace amounts of cycloaddition products). This qualitative assessment is not surprising, given the greater electron withdrawing capacity of the sulfone group. The enhanced reactivity of **6** has been illustrated by its reaction with terminal alkynes and enol ethers. The Diels-Alder reaction gave the resin-bound cycloaddition product **9** which was deprotected by 20% TFA in CH_2Cl_2 before the product **10** was cleaved from the solid support by base hydrolysis (Scheme 3).

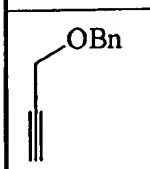
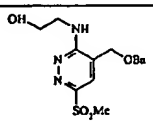
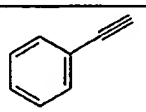
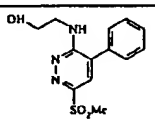
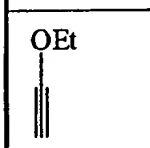
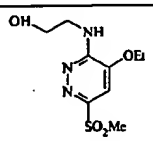
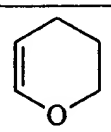
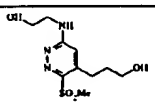
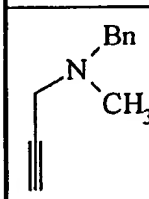
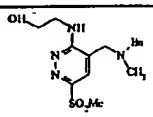
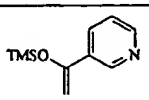
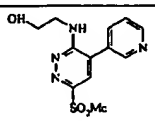
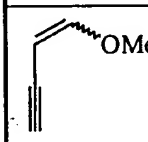
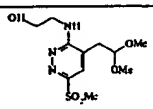
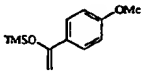
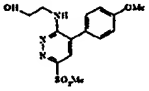


6 9 10

Scheme 3

Table 2 illustrates the variety of 3-amino-6-sulfonylmethyl-1,2-pyridazines that were synthesized in this reaction. Regioselectivity was achieved in the reactions of both **5** and **6**, which was resulted from the difference of the electron withdrawing ability between the tetrazines two substituted groups. The more electron-rich end of the dienophile tends to attach to the more electron-deficient carbon of the tetrazine. As the electron withdrawing ability is $-SO_2Me$ > -NBoc > -SMe, the conversion of SMe to SO_2Me inverts the electron deficiency at carbons in **5** and **6** (from C-3 in **5** to C-6 in **6**), turning over the regiochemical course of the reactions of **5** and **6**. Comparing the results in Table 1 and Table 2, we noted that both regioisomers of a 1,2-diazine could be synthesized by utilizing different tetrazines **5** or **6** (see Tables 1 and 2, **8e** *vs* **10e**).

Table 2. Diels-Alder Reactions of Polymer Supported Azadiene **6**

Dienophile[a]	Product	Yield of 10[b,c]	Dienophile[a]	Product	Yield of 10[b,c]
		10a 50%			10e 72%
		10b 72%			10f 30%
		10c 31%			10g 49%
		10d 66%			10h 22%

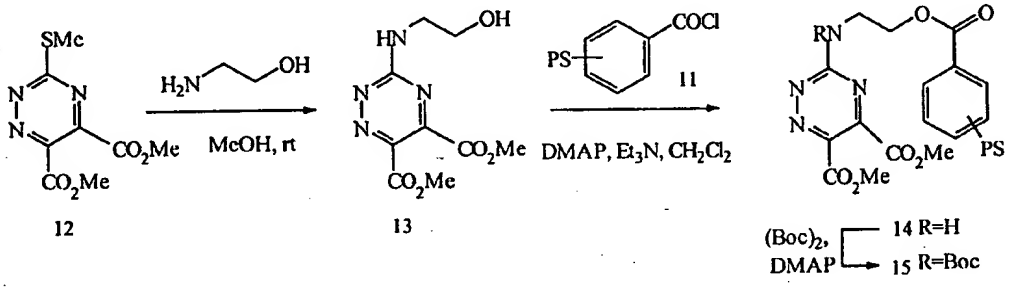
[a] The enol ethers were prepared from the correspondent ketones [$(TMS)_2NLi$, Et_3N, TMSCl, -78°C to rt, 12 h]. [b] The yields are based on the initial loading level of carboxylic acid on the polystyrene-CO_2H (7 steps overall). [c] A single regioisomer was obtained in all reactions.

In conclusion, we have described the synthesis of functionalized 1,2-diazines using the Diels-Alder reaction of 3,6-substituted 1,2,4,5-tetrazines on solid support. A wide range of electron-rich dienophiles were used, which permits the introduction of two of potentially four diversity elements on an aromatic scaffold. Subsequent nucleophilic aromatic substitution of the C-6 methyl sulfide/sulfone introduces the fourth diversity element.

Example 2

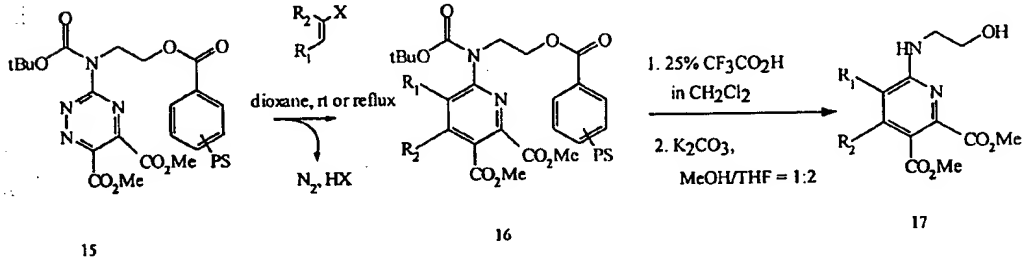
The preparation of the immobilized triazine **15** is summarized in Scheme 4, and utilized the readily available dimethyl 1,2,4-triazine-3-thiomethyl-5,6-carboxylate **12** (Benson, S.C.; Lee, L.; Snyder, J.K. *Tetrahedron Lett.* **1996**, *37*, 5061-5064). The choice of triazine **12** is based on its easily replaceable thiomethyl group which provides

easy access to other functional groups at the C-3 position. Nucleophilic aromatic substitution of the thiomethyl group with amino-ethanol (1.2 equiv., EtOH, rt, 12 h) afforded triazine **13** in 90% yield bearing the four-atom tether. Carboxylated resin **11** was prepared from polystyrene-CO_2H (commercially available from Advanced ChemTech) with excess of $(COCl)_2$ (4.0 equiv) refluxing in dry benzene for 12 h. The resulting resin was washed with dry benzene under argon and dried in vacuo to afford the acid chloride **11** as a light brown colored solid. The triazine nucleus was covalently linked to resin **11** through its acid chloride (cat. DMAP, Et_3N, CH_2Cl_2, rt, 48 h) to afford the immobilized amino triazine **14**. This material was made more electron deficient by the acylation of the secondary amine with $(Boc)_2O$(4 equiv, cat, DMAP, THF, rt, 16 h) producing the fully elaborated, immobilized triazine complex **15** as a yellow solid.



12 13

Scheme 4



15 16 17

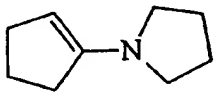
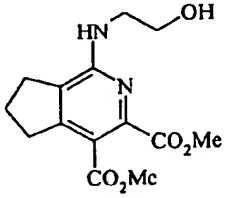
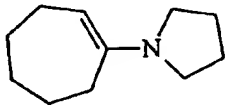
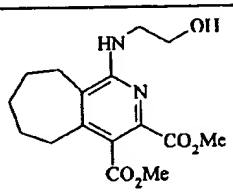
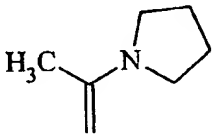
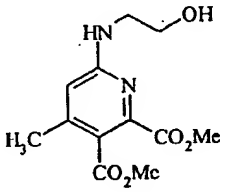
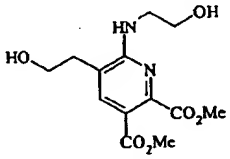
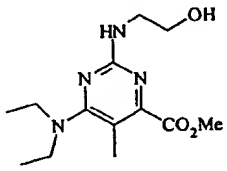
Scheme 5

The utility of azadiene complex **15** as electron deficient dienes in the inverse electron demand Diels-Alder reaction was examined (Scheme 5). The preliminary results of these studies are summarized in Table 1. Azadiene complex **15** was reacted with various electron-rich olefins in dioxane at room or elevated temperature to give the resin-bound cycloaddition-aromatization product **16**. The Boc group of **16** was removed with 25% TFA in CH_2Cl_2 before the product **17** was cleaved from the solid support by base hydrolysis (K_2CO_3, 1:2 MeOH-THF) (Scheme 5). A wide range of substituted

pyridines were synthesized in good to moderate overall yield and is based on the initial loading level of carboxylic acid on polystyrene-CO_2H, and represents 6 steps (Table 3).

In conclusion, we have described the synthesis of substituted pyridines using the Diels-Alder reaction of 1,2,4-triazines (and a 1,3-diazine) on solid support.

Table 3. Diels-Alder Reaction of Polymer Supported 1,2,4-triazine **15**

Dienophile	Reaction Conditions	Product	Yield of 17
	dioxane, rt		58%
	dioxane, rt		44%
	chloroform, reflux		35%
	dioxane, reflux		25% (4:1)
	dioxane, rt		66%

Example 3

An exemplary procedure for Diels-Alder reaction of a diene (e.g., a triazine) immobilized on solid support is as follows: the reactions of **15** were performed with 50

mg of resin using 10-20 equivalent of dienophile in 4.0 mL dioxane or chloroform for 24 h (r.t. or reflux). The resin was washed with CH_2Cl_2 (3 x 5.0 mL) to afford **16** which was then stirred slowlyin 4 mL 1:3 CF_3CO_2H-CH_2CL_2 for 1.5 h at room temperature. The resulting resin was washed with CH_2Cl_2 (3 x 5.0 mL) and 1:2 MeOH-THF (2 x 5.0 mL), and then stirred mildly in 3.0 mL 1:2 MeOH-THF with K_2CO_3 for 12 h. The reaction mixture was filtered and the filtrate was extracted with EtOAc. The organic phase was concentrated to dryness to afford **17**.

An exemplary procedure for Diels-Alder reaction of an immobilized tetrazine is as follows: a solid supported 3-amino-6-thiomethyl-1,2,4,5-tetrazine (50 mg diene-functionalized resin, 0.077 mmol) was reacted with 10 equivalents of dienophile in a suitable solvent (e.g., dioxane) (4.0 mL) for 24 hours. Temperature for the reaction ranged from room temperature to reflux temperature, depending on the reactivity of the diene and dienophile). The resin was then washed with dioxane (3 x 5.0 mL) and methylene chloride (3 x 5.0 mL), to remove impurities. The resin-bound heterocyclic product was then stirred in 2.5. mL of 1:4 trifluoroacetic acid:methylene chloride for 1 hour at room temperature, to remove the Boc protecting group. The resin was then washed with methylene chloride (3 x 5.0 mL) and 1:2 MeOH:THF (2 x 5.0 mL), and then gently stirred in 3.0 mL of MeOH:THF of potassium carbonate for 12 hours to cleave the product from the resin. The mixture was filtered and the filtrate extracted with ethyl acetate. The organic phase was concentrated to dryness to afford the heterocyclic product.

Similarly, a solid-supported 3-amino-6-methylsulfonyl-1,2,4,5-tetrazine (50 mg, 0.074 mmol) was refluxed with 10-20 equivalents of dienophile in 4 mL dioxane for 16 hours, followed by treatment with 20% TFA in methylene chloride for 1 hour. After washing with methylene chloride and MeOH-THF as above, and cleavage of the product from the solid support by treatment with potassium carbonate in MeOH-THF for 12 hours, the free product was obtained by filtration, extraction of the organic phase with ethyl acetate, and concentration of the ethyl acetate extract to afford the product.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. Other embodiments are within the following claims.

The contents of all references cited herein are hereby incorporated by reference.

What is claimed is:

1. A method for synthesizing an aromatic heterocycle, comprising

contacting a dienophile with a diene under conditions such that a Diels-Alder reaction occurs between said diene and said dienophile, wherein said diene comprises a heteroatom; and

allowing said aromatic heterocycle to form;

wherein at least one of said diene or said dienophile is bound to a solid support.

2. The method of claim 1, wherein said diene is bound to a solid support.

3. The method of claim 2, wherein said diene is bound to said solid support through a cleavable linker.

4. The method of claim 1, wherein the diene is a heterocycle.

5. The method of claim 4, wherein the diene is selected from the group consisting of diazines, triazines, and tetrazines.

6. The method of claim 1, wherein the diene is electron-rich.

7. The method of claim 6, wherein the Diels-Alder reaction is an inverse electron demand Diels-Alder reaction.

8. The method of claim 1, wherein the dienophile is selected from the group consisting of enamines, ynamines, enol ethers, imidates, imines, thiocarbonyls, enol esters, thioenol ethers, alkynes, and vinylstannanes.

9. The method of claim 1, wherein the solid support is a polymer resin.

10. The method of claim 1, wherein the heteroatom is nitrogen.

11. A method for synthesizing a solid-supported aromatic heterocycle, comprising

contacting an electron-rich dienophile with a diene under conditions such that a Diels-Alder reaction occurs between said diene and said dienophile to form a Diels-Alder adduct, wherein said diene comprises a heteroatom, and wherein at least one of said diene or said dienophile is bound to a solid support; and

subjecting said Diels-Alder adduct to conditions such that said adduct decomposes to form a solid-supported aromatic heterocycle.

12. The method of claim 11, wherein the step of decomposing the Diels-Alder adduct comprises heating the Diels-Alder adduct.

13. The method of claim 11, wherein the decomposing step comprises eliminating from the Diels-Alder adduct a leaving group selected from the group consisting of alcohols and amines.

14. The method of claim 11, wherein said aromatic heterocycle is bound to said solid support through a cleavable linkage.

15. The method of claim 13, wherein said cleavable linkage is an ester linkage.

16. The method of claim 14, comprising the further step of releasing said aromatic heterocycle from said solid support by cleaving said cleavable linkage.

17. A method for synthesizing a diazine, comprising

reacting an electron-rich dienophile and a tetrazine bound to a solid support, under conditions such that a Diels-Alder reaction occurs between said dienophile and said tetrazine; and

allowing said diazine to form.

18. The method of claim 17, wherein said dienophile is selected from the group consisting of enamines, enol ethers, alkynes and ynamines.

19. The method of claim 17, wherein the tetrazine is a 1,2,4,5-tetrazine.

20. A method for synthesizing a triazine, comprising

reacting an electron-rich dienophile and a tetrazine bound to a solid support, under conditions such that a Diels-Alder reaction occurs between said dienophile and said tetrazine; and

allowing said triazine to form.

21. The method of claim 20, wherein the triazine is a 1,2,4-triazine.

22. A method for synthesizing a library of aromatic heterocycles, the method comprising reacting a dienophile and a diene under conditions such that a Diels-Alder reaction occurs between said diene and said dienophile, wherein said diene comprises a heteroatom, and wherein at least one of said dienophile and said diene is provided as a variegated population; and

allowing said library of aromatic heterocycles to form;

wherein at least one of said diene and said dienophile is bound to a solid support.

23. A method for synthesizing a pyridine, comprising

reacting an electron-rich dienophile and a triazine bound to a solid support, under conditions such that a Diels-Alder reaction occurs between said dienophile and said triazine; and

allowing said pyridine to form.

24. The method of claim 23, wherein said pyridine is a substituted pyridine.

25. The method of claim 23, wherein said dienophile is selected from the group consisting of enamines, enol ethers, ynamines and alkynes.

26. A library of aromatic heterocycles represented by the formula S-L-A, in which

S is a solid support;

L is absent or, if present, is a linking moiety; and

A is an aromatic heterocyclyl moiety.

27. The library of claim 26, wherein the solid support is a polymer resin.

28. The library of claim 26, wherein the aromatic heterocyclyl moiety is selected from the group consisting of pyridyl, 1,2-diazinyl, 1,3-diazinyl, and 1,4-diazinyl.